

Association Between Adiponectin Levels with Markers of Atherosclerosis In Patients with Rheumatoid Arthritis

Tanggo Meriza¹, Harry Isbagio¹, Rahmad Mulyadi², Murdani Abdullah³

¹ Rheumatology Division Department of Internal Medicine Medical Faculty University of Indonesia Jakarta.

² Department of Radiology Medical Faculty University of Indonesia Jakarta.

³ Gastroenterology and Hepatology Division Department of Internal Medicine Medical Faculty University of Indonesia Jakarta.

ABSTRACT

Background: Several studies have shown that atherosclerosis underlying processes of Cardiovascular disease (CVD), increased in rheumatoid arthritis (RA) and occurred early (premature). The cause of accelerated atherosclerosis in RA are still unknown. Adipokines have known that the adipokines play a role in the pathophysiology of RA and CVD. Accumulation of visceral fat associated with dysregulation of adipokines that influence the development of the atherosclerotic and disruption plaque. Obesity and pathological changes in fat mass and fat dysfunction as well as a change in the pattern of secretion of proinflammatory adipokines, may have a correlation between heart disease and rheumatic diseases. Adiponectin is one of the most widely-studied adipokines. In RA, adiponectin is involved in the pathophysiology of RA that produces of various proinflammatory and prodestructive molecules. So far, adiponectin has been known to provide anti-atherosclerotic effects in patients with non-RA. But, several recent studies in RA patients get opposite results in which increased levels of adiponectin are associated with increased prevalence of atherosclerosis. The effect of adiponectin on atherosclerosis in patient with RA is still unknown.

Objective: to determine the relationship of adiponectin with atherosclerosis in patients with rheumatoid arthritis.

Methods: This is a cross-sectional study conducted on outpatients of the rheumatology clinic at Cipto Mangunkusumo General Hospital from January until April, 2013. Subjects consisted of 50 patients were diagnosed based on ACR 1987/EULAR 2010 criteria. The collection of data obtained by consecutive sampling and evaluated the patients' medical data that included age, long-suffering of RA, body mass index (BMI), lipid profile, rheumatoid factor levels, levels of anti-cyclic citrullinated peptide (anti-CCP), C-reactive protein (CRP), erythrocyte sedimentation rates (ESR), blood pressure, fasting blood glucose, 2 hour post prandial blood glucose, ECG, examination of serum adiponectin levels and bilateral carotid ultrasound to measure the carotid artery intima media thickness.

Results: From the results of the 50 patients studied, obtained 28 (56%) of patients had increased levels of adiponectin. Atherosclerosis was found in 13 (26%) subjects. The median value was $9.46 \mu\text{g} / \text{ml}$ with the lowest levels of $4 \mu\text{g}/\text{ml}$ and the highest levels of $24 \mu\text{g}/\text{ml}$. The Spearman's test showed no

significant correlation between adiponectin serum and atherosclerosis in patients with RA ($p = 0.706$ and $r = 0.055$). The analysis results of the correlation of adiponectin with atherosclerosis based on age, disease duration, ESR, rheumatoid factor, DAS 28, CRP, BMI, dyslipidemia showed no significant correlation.

Conclusion : From this study, researchers found no statistically significant correlation between adiponectin levels with marker of atherosclerosis (CMT) in patients with rheumatoid arthritis

Keywords : Adiponectin, Atherosclerosis

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterized by the involvement of articular and extra-articular. Cardiovascular disease (CVD) is the most important cause of mortality and morbidity of patients with RA.¹ CVD causes almost 50% to more deaths in patients with RA.² Several studies have shown that atherosclerosis underlying processes of CVD, increased in RA and occurred early (premature). But the cause of accelerated atherosclerosis in RA are still unknown. The increased risk of CVD in RA can not be fully explained by traditional risk factors such as age, sex, smoking, hypertension or type 2 diabetes (DM).³

In contrast to the general population, the risk of CVD in patients with RA particularly elevated in younger patients and female gender. Low body mass index ($<20 \text{ kg}/\text{m}^2$) was also associated with a higher cardiovascular mortality. This may be correlated with increased inflammatory cytokines leads to a catabolic process.¹

It remains unclear how the traditional risk factors interact with non-traditional risk factors to increase CVD in RA. However, some traditional risk factors, such as: men, sex, smoking and previous cardiovascular events, seems to have a relationship with the occurrence of CVD in patients with RA, but its contribution to the rate of CVD seems weak.⁴

In addition to traditional risk factors, chronic systemic inflammation has been shown to be an important factor in the development of atherosclerosis. Increased systemic inflammation in patients with RA is one of the non-traditional factors that will increase the cardiovascular risk in RA.⁵ RA is a prototype of a chronic systemic

inflammatory disease. And interestingly, there are similarities between the inflammatory pathways in atherosclerosis and RA.¹

Although traditional risk factors are also involved in the pathogenesis of cardiovascular disease in patients with RA, but does not fully explain how the increased cardiovascular risk in this population. Classical risk factors such as obesity might explain the increased risk of CVD in patients with RA.⁶ It is well known that adipokines play a role in the pathophysiology of RA and CVD. Visceral fat accumulation associated with dysregulation of adipokines that influence the development of atherosclerotic and disruption plaque. Obesity and pathological changes in fat mass and fat dysfunction as well as a change in the pattern of secretion of proinflammatory adipokines, could be one of the link between heart disease and rheumatic diseases. Indeed, the incidence of CVD is increased in obese individuals with rheumatic disorders.⁷

Since the discovery of leptin in 1994, adipose tissue is no longer considered as a passive reservoir for storage energy.⁸ Adipose tissue is an endocrine and metabolic organ that is very active and produce large amounts of bioactive peptides.^{8,9} These molecules known as adipokines and substantially can modulate the metabolic cardiovascular risk factors including insulin resistance and atherogenesis, and inflammatory and immune respons. Leptin and adiponectin are the most studied adipokines.⁸

At the individual non-RA, adiponectin is anti-inflammatory, anti-atherogenic, anti-diabetic,^{11, 12, 13} repair and production of metabolic risk decrease with increasing adiposites.^{8, 10} High levels adiponectin are favorable factor because it will decrease the progression of atherosclerosis.¹⁴

The above findings are very opposite, considering the increased adiponectin level in RA, while the incidence of atherosclerosis in RA also increased. In contrast to the properties of adiponectin as an anti-inflammatory in a non-RA population. In contrast to RA, adiponectin is involved in the pathophysiology of RA, which produce a variety of proinflammatory and prodestructive molecule.^{8, 15-18} Most studies in patients with RA have shown an increase in the serum concentration of adiponectin, and adiponectin is also produced in the inflamed joints.^{8, 15, 19} Several studies have also shown that adiponectin is involved in the development of RA.^{8, 15-18, 20, 21} These finding support the involvement of adiponectin in the immune response in RA. Adiponectin may play a role in the pathophysiology of rheumatoid arthritis that adiponectin can be a potential new therapeutic targets by performing inhibition of adiponectin.²²

Is the RA could modify the effect of adiponectin on risk of atherosclerosis, is currently unknown. Therefore, this study required for the management of RA and inhibition of adiponectin on the possible use of RA (as a new therapeutic target),¹⁸ so that can explain how the inhibitory effect of adiponectin on cardiovascular risk in patients with RA. Adiponectin has anti-inflammatory effects on blood vessels and on metabolic pathways and is a cardiovascular protective factor. Therefore, when inhibition therapy of adiponectin is done systematically, may provide cardiovascular consequences

unintended opposite. Giving inhibitor of adiponectin through intra-articular pathways is more advisable because theoretically it can limit the proinflammatory effects of adiponectin on the joints but do not eliminate the anti-inflammatory effects on blood vessels and cardiovascular.²³

Carotid Intima-Media Thickness (CIMT) is an important marker for early subclinical atherosclerosis. CIMT is also a strong predictor for future cardiovascular events in individuals RA and non-RA.^{24, 25} In individuals non RA, adiponectin levels are inversely related to CIMT, where low adiponectin levels will increase progression of atherosclerosis, thereby increasing the risk of cardiovascular disease (CVD). Shargorodsky et al found that serum levels of adiponectin are associated with early atherosclerosis assessed by CIMT in obese patients non-RA.¹⁴ So adiponectin is also an independent predictor marker of early subclinical atherosclerosis in obese individuals non-RA. Measurement technique of Carotid IMT can be considered as a valid marker of early atherosclerosis in asymptomatic patients and is a predictor of mortality and morbidity of the cardiovascular disease.²³⁻²⁵

METHODS

Study Design

The research design was a cross-sectional study design using primary data obtained from anamnesis, physical examination, and investigation. The study was conducted between January until April 2013, at Polyclinic Rheumatology, Department of Internal Medicine, Cipto Mangunkusomo Hospital (RSCM), Jakarta.

Patients

Total sample consisted of 50 patients with new and old RA who have been diagnosed RA based on the ACR 1987/EULAR 2010 criteria who visited rheumatology outpatient clinic at the Cipto Mangunkusomo Hospital (RSCM). Sampling were collected using a consecutive sampling method. The inclusion criteria were patients with RA who fulfilled ACR 1987/EULAR 2010 criteria, age > 16 years when diagnosed and are willing to follow the study. The exclusion criteria were patients with type 2 diabetes, hypertension, patients with a history of myocardial infarction, stroke or peripheral artery disease and treatment with ACE-inhibitor drugs.

Assesments

Necessary data were collected by performing anamnesis, physical examination, laboratory tests and carotid ultrasound. Included in the assessment were clinical variables such as age, disease duration of RA, Body Mass Index (BMI), lipid profile, rheumatoid factor levels, levels of anti-CCP, levels of anti CRP, and ESR, blood pressure, fasting blood glucose, 2-hour post-prandial, ECG, and serum adiponectin levels examination. The concentration of serum adiponectin [$\mu\text{g}/\text{ml}$] were measured using Human Adiponectin ELISA kit according to the manufacturers' instructions. The normal value of total adiponectin concentration in plasma 3.58 to 9.66 $\mu\text{g}/\text{ml}$ for women and 2.54 to 6.06 $\mu\text{g}/\text{ml}$ for males. Carotid ultrasound is done by one person radiologist using ultrasound

B-mode brand Philips Sonos 5500. Standard normal values of Carotid Intima-Media Thickness (CMT) is ≤ 1.0 mm.²⁶

Statistical Analysis

The data collected were analyzed using computer applications with SPSS version 15.0. Descriptive and analytical data will be presented in the form of text, tables, and pictures as appropriate.

RESULTS

Of the 50 subjects involved in this study, 56% (28 patients) subjects had high serum adiponectin levels. Mean adiponectin levels could not be determined because the data distribution is not normal. While the median value is $9.46 \mu\text{g} / \text{ml}$ with the lowest levels of $4 \mu\text{g} / \text{ml}$ and the highest levels of $24 \mu\text{g} / \text{ml}$. The total of male subject (2 patients) have high adiponectin levels.

Bivariate analysis was done to see the correlation of independent variabel, namely adiponectin levels with the dependent variable, namely atherosclerosis. All variables were analyzed had a abnormal distribution, so the Spearman correlation statistical test was used. The results of correlation test between adiponectin levels and atherosclerosis showed a very weak correlation Alt value of $p=0706$ and $r=0.055$. Furthermore, the relationship of adiponectin levels and atherosclerosis were analyzed by age, disease duration, ESR, rheumatoid factor, DAS 28, CRP, BMI, and dyslipidemia, but none of which showed significant results.

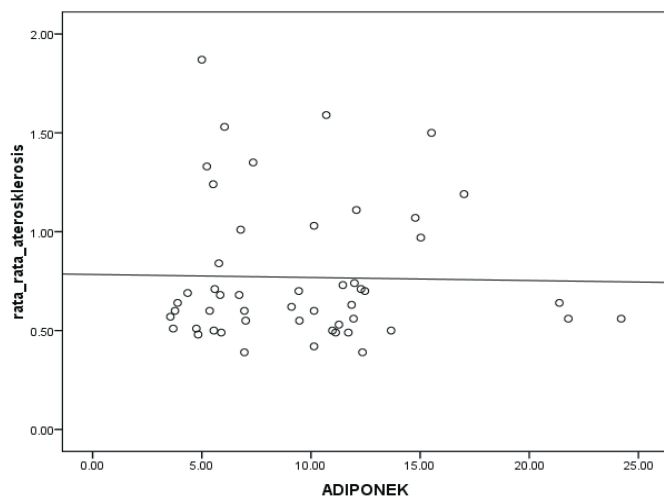


Figure 2. The relationship between the adiponectin levels and average value of atherosclerosis

DISCUSSION

In this study, obtained 28 subjects (56%) had high levels of adiponectin. With a higher proportion (56%) indicate that adiponectin plays an important role in the pathogenesis of RA.

At the individual non-RA, adiponectin is inversely related to atherosclerosis. Adiponectin has been shown to play a key role in obesity, inflammation, insulin resistance and atherosclerosis, but little is known about their contribution to individual with RA. As shown in this study, the adiponectin levels in patients with RA showed no-significant correlation

with the intima media thickness of the carotid artery. It is a marker of early atherosclerosis. The relationship of adiponectin and atherosclerosis were then analyzed by age, disease duration, ESR, rheumatoid factor, DAS 28, CRP, BMI, dyslipidemia, but none of which showed significant results. The results of this study have the same results with the results obtained by Gonzalez et al.^{25,27} and Dessein et al.²², that there is no correlation between adiponectin and intima media thickness of the carotid artery.

Serum concentration of adiponectin was not associated with atherosclerosis and cardiovascular event rates in RA.^{7,20,27,28} It should be noted that in this case, the presence of autoimmunity may change the effects of adiponectin on metabolic risk and cardiovascular disease.²²

So also with the incidence of CVD in RA, because not all patients with RA will experience the same CVD events. This difference is thought to be caused by the presence of genetic susceptibility to atherosclerosis which may also play a role. HLA-DRB1*0404 is a predisposing gene for RA and is associated with more severe RA disease. RA patients with HLA-DRB1*0404 gene-shared epitope-positive have a higher cardiovascular mortality compared with the epitope-negative.²⁹

Patients with RA had an increased prevalence of premature atherosclerosis and insulin resistance, are associated with accelerated coronary atherosclerosis.²⁸ Prevalence of CVD in RA may be higher than DM type 2.³⁰ This study found no correlation between adiponectin with other cardiovascular risk factors such as age, disease duration, ESR, rheumatoid factor, DAS 28, CRP, BMI, and dyslipidemia. Other researchers also found that adiponectin was not correlated with several risk factors for atherosclerosis such as coronary calcium scoring²⁸, HOMA IR,^{12,28} total cholesterol, LDL kolesterol levels, systolic and diastolic blood pressure¹². However, adiponectin correlated negatively with high levels of inflammation and plasma glucose.¹² Rho et al also found high concentrations of adiponectin in patients with RA, but adiponectin was not associated with coronary calcification and insulin resistance.²⁸

In another study Gonzalez obtained the different results. High levels of inflammation associated negatively with circulating adiponectin, and low adiponectin concentration is more correlated independently with an overview of the metabolic syndrome (dyslipidemia and high plasma glucose levels). These findings are similar to those reported in non-RA subjects, and these increase the possibility that adiponectin contributes to atherogenesis in RA and subsequently involve in cardiovascular disease in patients with RA.¹²

Adiponectin has been associated as a protective factor for atherosclerosis in individual non-RA. However, in this study found no relationship between adiponectin and atherosclerosis. This may be due in patients with RA, the effect of adiponectin in atherosclerosis may be obscured by other inflammatory mediators that have pro-atherogenic effect whose levels are elevated in RA.

Adiponectin play an important role in the pathogenesis of RA, but plays small role in the pathogenesis of subclinical atherosclerosis in RA and inhibition of systemic adiponectin

would not change the overall cardiovascular risk in patients with RA.²² In the context of adiponectin as a therapeutic target for RA, this provides new opportunities for the provision of adiponectin inhibitors through the systemic pathways. Because adiponectin is not associated with atherosclerosis in patients with RA, we don't need to worry about giving systemic inhibitors of adiponectin will eliminate the protective effect of adiponectin in the cardiovascular. So that the provision of adiponectin inhibitors can be done through the systemic pathways.

Another consequence of the results of this study also shows that levels of adiponectin have not been able to replace the use of ultrasound to measure CIMT as a predictor of atherosclerotic events in particular and the incidence of cardiovascular disease is common in patients with RA who do not exhibit clinical symptoms of cardiovascular disease.

The management to prevent CVD should be supported as much as possible. The main cause abnormal accumulation of fat mass and adiponectin dysfunction is poor nutrition and lifestyle habits, such as overeating and lack of physical activity. Therefore, the first approach to manage CVD in rheumatic disease is lifestyle modification and other therapeutics intervention that lead to decrease of fat mass and fat dysfunction to decrease cardiovascular mortality in patients with RA.⁷

From the data above, we need other efforts to prevent CVD. Therefore, we also need to know the other risk factors that will lead and aggravate cardiovascular disease in RA. In general population, cardiovascular mortality the same as RA was also associated with CRP and ESR.¹ TNF- α and IL-6 is a pro-inflammatory cytokine that also show the independent predictive role for cardiovascular events in the future.²⁹ These cytokines have an important role in the pathogenesis of RA and have high concentration in patients with RA. In addition, the duration and disease activity, the involvement of many joints, the presence of rheumatoid factor (RF), rheumatoid nodules and extra-articular manifestations are also a specific determinant of CVD events in patients with RA.³¹ All of this suggests that systemic inflammation is not treated it can cause damage before injure the joints. And long-term exposure to systemic inflammation increases the risk of CVD. So the use of anti-rheumatic drugs are effective in suppressing the inflammation that will be able to reduce the risk of CVD events and one of prevention CVD in RA.¹ Besides, it is also required close monitoring of serum lipid levels that would changes adiponectin production or inhibit its effect in RA.²²

Limitations of Research

One of limiting factors in this study was adiponectin which had measured in this study are total adiponectin. Whereas adiponectin has several isoforms that may have a different biological function, and there is the opposite function. Although more studies show pro-inflammatory function of adiponectin in patients with RA, but the relationship between adiponectin and RA is not fully understood yet. So that further studies are needed which refers to the role of adiponectin isoforms.

Serum adiponectin levels may not be the same as the joint adiponectin levels.²⁰ Adiponectin produced locally by intra-articular adipocytes, may play a role in the degradation of extracellular matrix components.¹⁵ These raise an assumption that the serum adiponectin levels may not reflect the actual activity of adiponectin in a particular tissue. Alternatively, increased production of adiponectin in autoimmune disease or in chronic inflammatory conditions may be secondary to inflammation - due to the catabolic response that occurs in RA.^{15,32,33}

CONCLUSION

In this study, we found no statistically significant correlation between adiponectin levels with marker of atherosclerosis (CIMT) in patients with rheumatoid arthritis

REFERENCE

1. Ozbalkan Z, Efe C, Cesur M, Ertek S, Nasiroglu N, Berneis K et al. An update on the relationships between rheumatoid arthritis and atherosclerosis. *Atherosclerosis* 2010;212:377-82
2. S. M. Naz and D. P. Symmons, Mortality in established rheumatoid arthritis, *Best Practice & Research Clinical Rheumatology*. 2007;21:871-83.
3. del-Rincón I, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthritis Rheum*. 2001;44(12):2737-45.
4. Gonzalez A, Maradit-Kremers H, Crowson CS, et al. Do cardiovascular risk factors confer the same risk for cardiovascular outcomes in rheumatoid arthritis patients as in non-rheumatoid arthritis patients? *Ann Rheum Dis* 2008;67:64-9.
5. John H, Kitas G, Toms T, Goodson N. Cardiovascular co-morbidity in early rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2009;23:71-82.
6. N. Erb, A. V. Pace, K. M. J. Douglas, M. J. Banks, and G. D. Kitas, Risk assessment for coronary heart disease in rheumatoid arthritis and osteoarthritis, *Scandinavian Journal of Rheumatology*. 2004;33:293-9.
7. Scotece M, Conde J, Gomez R, et al. Role of Adipokines in Atherosclerosis: Interferences with Cardiovascular Complications in Rheumatic Disease. *Mediators of Inflammation* 2012; Article ID 125458, 1-14.
8. Gimeno RE, Klamann LD. Adipose tissue as an active endocrine organ: recent advances. *Curr Opin Pharmacol* 2005;5:122-8
9. Gomez R, Conde J, Scotece M, Gomez-Reino JJ, Lago F, Gualillo O. What's new in our understanding of the role of adipokines in rheumatic diseases? *Nat Rev Rheumatol* 2011;7:528-36.
10. T. Kadowaki, T. Yamauchi, N. Kubota, K. Hara, K. Ueki, and K. Tobe, Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome, *Journal of Clinical Investigation*. 2006;116:1784-92.
11. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nat Rev Immunol* 2006;6:772-83.
12. Gonzalez-Gay MA, Llorca J, Garcia-Unzueta MT, Gonzalez-Juanatey, De Matias JM, Martin J et al. High-grade inflammation, circulating adiponectin concentrations and cardiovascular risk factor in severe rheumatoid arthritis. *Clin Ex Rheum* 2008;26:596-603.
13. Scotece M, Conde J, Lopez V, Lago F, Pino J, Gomez-Reino JJ et al. Adiponectin and leptin : New Targets in inflammation. *Basic Clin Pharm Toxicol*. 2013 Doi :10.1111/bcpt.12109. Page 1 – 6.
14. Shargorodsky M, Boaz M, Goldberg Y, Matas Z, Gavish D, Fux A et al. Adiponectin and vascular properties in obese patients: is it a novel biomarker of early atherosclerosis ? *Int J Obes* 2009;33:553-8.

15. Krysiak R, Handzlik-Orlik G, Okopien B. The role of adipokines in connective tissue diseases. *Eur J Nutr* 2012;51:513-28.
16. Frommer KW, Schäffler A, Büchler C, Steinmeyer J, Rickert M, Rehat Steffen et al. Adiponectin isoforms: a potential therapeutic target in rheumatoid arthritis ? *Ann Rheum Dis* 20012;71:1724-32
17. Ehling A, Scäffler A, Herfarth H et al. The potential of adiponectin in driving arthritis *J Immunol* 2006;176:4468-78
18. Frommer KW, Zimmermann B, Meier FMP, Schroder D, Heil M, Schäffler A et al. Adiponectin-Mediated Changes in Effector Cells Involved in the Pathophysiology of Rheumatoid Arthritis. *Arthritis Rheum* 2010;62:2886-99.
19. Rho YH, Solus J, Sokka T, Oeser A, Chung CP, Gebretsadik T et al. Adipocytokines Are Associated With Radiographic Joint Damage in Rheumatoid Arthritis. *Arthritis Rheum*. 2009;60:1906-13.
20. Giles JT, van der Heijde DM, Bathon JM. Association of circulating adiponectin levels with progression of radiographic joint destruction in rheumatoid arthritis. *Ann Rheum Dis* 2011;70:1562-8.
21. Klein-Wieringa IR, van der Linden MPM, Knevel R, Kwekkeboom JC, van Beelen E, Huizinga TWJ et al. Baseline Serum Adipokine Levels Predict Radiographic Progression in Early Rheumatoid Arthritis. *Arthritis Rheum* 2011;63:2567-74.
22. Dessein PH, Norton GR, Badenhorst M, Woodiwiss AJ, and Solomon A. Rheumatoid Arthritis Impacts on the Independent Relationships between Circulating Adiponectin Concentrations and Cardiovascular Metabolic Risk. *Mediators of Inflammation* 2013, Article ID 461849, 9 pages.
23. Giles JT, Allison M, Bingham CO, 3rd, et al. Adiponectin is a mediator of the inverse association of adiposity with radiographic damage in rheumatoid arthritis *Arthritis Rheum* 2009;61:1248-56
24. Rho YH, Chung CP, Oeser A, Solus J, Asanuma Y, Sokka T et al. Inflammatory Mediators and Premature Coronary Atherosclerosis in Rheumatoid Arthritis. *Arthritis Rheum*. 2009;61:1580-5.
25. Gonzalez-Juanatey C, Llorca J, Martin J, Gonzalez-Gay M. Carotid Intima-Media Thickness Predicts the Development of Cardiovascular Events in Patients with Rheumatoid Arthritis. *Semin Arthritis Rheum* 2009;38:366-71.
26. van-Gaalen F, Visser H, Huizinga TWJ. A comparison of the diagnostic accuracy and prognostic value of the first and second anti-cyclic citrullinated peptides (CCP1 and CCP2) autoantibody tests for rheumatoid arthritis. *Ann Rheum Dis*. 2005;64:1510-12.
27. Gonzalez Gay MA, Gonzalez Juanatey C, Rodriguez-Rodriguez L, Miranda-Filloy JA, Martin J, Llorca J. Lack of association between adipokines and ghrelin and carotid intima-media thickness in patients with severe rheumatoid arthritis. *Clinical and Experimental Rheumatology* 2011;29:358-9.
28. Rho YH, Chung CP, Solus JF, Raggi P, Oeser A, Gebretsadik T et al. Adipocytokines, Insulin Resistance, and Coronary Atherosclerosis in Rheumatoid Arthritis. *Arthritis Rheum* 2010;62:1259 – 64.
29. Gonzalez-Gay MA, Gonzalez-Juanatey C, Lopez-Diaz MJ, et al. HLA-DRB1 and persistent chronic inflammation contribute to cardiovascular events and cardiovascular mortality in patients with rheumatoid arthritis. *Arthritis Rheum* 2007;15(57):125-32.
30. Van Halm VP, Peters MJ, Voskuyl AE, et al. Rheumatoid arthritis versus diabetes as a risk factor for cardiovascular disease: a cross-sectional study, the CARRE Investigation. *Ann Rheum Dis* 2009;68:1395-400.
31. Goodson NJ, Symmons DP, Scott DG, et al. Baseline levels of C-reactive protein and prediction of death from cardiovascular disease in patients with inflammatory polyarthritis: a ten-year followup study of a primary care-based inception cohort. *Arthritis Rheum* 2005;52:2293-9.
32. Fantuzzi G. Adiponectin and inflammation : Consensus and controversy. *J Allergy Clin Immunol* 2008;121:326-30
33. Behre CJ. Adiponectin: a defense protein in catabolism. *J Allergy Clin Immunol* 2008;122:1236